Monitoring Parameters for Chemotherapy and Immunotherapy

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Disclosure

• I have nothing to disclose. There are no relevant financial or personal relations with any ACCME defined commercial interests.
Objectives

- Identify chemotherapy and immunotherapy drug classes
- Recognize lab monitoring parameters prior to treatment initiation and during treatment
- Discuss the most common toxicities associated chemotherapy and immunotherapy
- Understand clinical strategies used to manage or reduce risk of potential toxicities
Chemotherapy

• Chemical agents utilized to inhibit the growth of malignant cells
  – Destroy cancer cells
  – Prevent further cancer cell replication

• Goals of chemotherapy
  – Curative: eliminate all cancer cells to attain a permanent cure
  – Adjuvant: supportive therapy post primary treatment to prevent recurrence
  – Neoadjuvant: therapy prior to primary treatment to reduce tumor size
  – Palliative: symptom management or slow disease progression
Chemotherapy Drug Classes

• **Alkylating agents**
  - Alkyl sulfonates
  - Aziridines
  - Nitrogen mustards
  - Nitrosoureas
  - Platinum agents
  - Triazenes/Methylating agents

• **Antimetabolites**
  - DNA hypomethylating agents
  - Folate antagonists
  - Pyrimidine analogs
  - Purine analogs
  - Miscellaneous: hydroxyurea

• **Antimicrotubular agents**
  - Epothilones
  - Halichondrin B analogs
  - Taxanes
  - Vinca alkaloids

• **Antitumor antibiotics**
  - Anthracyclines
  - Actinomycins
  - Miscellaneous: bleomycin, mitomycin, mitoxantrone

• **Topoisomerase inhibitors**
  - Topoisomerase I inhibitors
  - Topoisomerase II inhibitors
    - Anthracyclines
Chemotherapy Mechanism of Action

<table>
<thead>
<tr>
<th>Phase</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>$G_1$</td>
<td>DNS synthesis preparation</td>
</tr>
<tr>
<td>$S$</td>
<td>DNA synthesis</td>
</tr>
<tr>
<td>$G_2$</td>
<td>Mitosis preparation</td>
</tr>
<tr>
<td>$M$</td>
<td>Mitosis and cell division</td>
</tr>
<tr>
<td>$G_0$</td>
<td>Resting state</td>
</tr>
</tbody>
</table>

M Phase Specific
Antimicrotubule Agents
Inhibit function of microtubules
- Epothilones
- Halichondrin B analogue
- Taxanes
- Vinca alkaloids

Topoisomerase II Inhibitors
Block topoisomerase function (unwinding DNA)
- Anthracyclines
- Epipodophyllotoxins

Agents Affecting Multiple Phases of the Cell Cycle
Antitumor Antibiotics
Induce DNA Lesions, inhibit topoisomerase, among other effects
- Bleomycin
- Dactinomycin
- Mitomycin

Cell Cycle Independent
Alkylating Agents
Crosslink guanine nucleobases in DNA
- Alkyl sulfonates
- Ethylenimines
- Nitrogen mustard
- Nitrosureas
- Platinum analogues
- Triazenes

S Phase Specific
Antimetabolites
Inhibit DNA synthesis
- Folate antagonists
- Purine analogues
- Pyrimidine analogues
- Hydroxyurea

Topoisomerase II Inhibitors
Block topoisomerase function (unwinding DNA)
- Anthracyclines
- Epipodophyllotoxins
Chemotherapy Toxicity Overview

**Patient**
- Cancer type
- Comorbidities
- Organ function
- Performance status

**Chemotherapy**
- Drug mechanism of action
- Drug dose
- Drug schedule
- Chemotherapy combination

**Toxicities**
- Myelosuppression
- Hepatic
- Renal
- Cardiovascular
- Pulmonary
- Gastrointestinal
- Neurological
- Dermatological
- Immune related
- Secondary malignancy
Lab Monitoring Overview

- Complete blood count (CBC) with differential
  - Required prior to almost all chemotherapy orders
  - Evaluating absolute neutrophil count (ANC), hemoglobin, hematocrit, and platelets
- Liver function tests (LFTs)
- Serum creatinine (SCr)
- Left ventricular ejection fraction (LVEF)
- Pulmonary function tests (PFTs)
- Electrolytes
- Pregnancy test
## LFT Monitoring for Chemotherapy

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>LFT Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ado-trastuzumab</strong> <em>(Kadcyla)</em></td>
<td>Cytarabine <em>(Ara-C)</em></td>
</tr>
<tr>
<td>Bendamustine <em>(Treanda)</em></td>
<td>Doxorubicin Liposomal <em>(Doxil)</em></td>
</tr>
<tr>
<td><strong>Ado-trastuzumab</strong> <em>(Kadcyla)</em></td>
<td>Irinotecan Liposomal <em>(Onivyde)</em></td>
</tr>
<tr>
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<td>Pemtrexed <em>(Alimta)</em></td>
</tr>
<tr>
<td><strong>Bortezomib</strong> <em>(Velcade)</em></td>
<td>Dacarbazine <em>(DTIC-Dome)</em></td>
</tr>
<tr>
<td><strong>Bortezomib</strong> <em>(Velcade)</em></td>
<td>Epirubicin <em>(Ellence)</em></td>
</tr>
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<td><strong>Bortezomib</strong> <em>(Velcade)</em></td>
<td>Irinotecan <em>(Camptosar)</em></td>
</tr>
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<td><strong>Bortezomib</strong> <em>(Velcade)</em></td>
<td>Pralatrexate <em>(Folotyn)</em></td>
</tr>
<tr>
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<td>Daunorubicin <em>(Cerubidine)</em></td>
</tr>
<tr>
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<td>Etoposide <em>(Etopophos)</em></td>
</tr>
<tr>
<td><strong>Brentuximab</strong> <em>(Adcetris)</em></td>
<td>Methotrexate</td>
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<td>Trabectedin <em>(Yondelis)</em></td>
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<td>Decitabine <em>(Dacogen)</em></td>
</tr>
<tr>
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<td><strong>Gemtuzumab</strong> <em>(Mylotarg)</em></td>
</tr>
<tr>
<td><strong>Carfilzomib</strong> <em>(Kyprolis)</em></td>
<td>Mitoxantrone <em>(Novantrone)</em></td>
</tr>
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<td><strong>Carfilzomib</strong> <em>(Kyprolis)</em></td>
<td>Vinblastine <em>(Velban)</em></td>
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<td>Ifosfamide <em>(Ifex)</em></td>
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</tr>
<tr>
<td><strong>Cabazitaxel</strong> <em>(Jevtana)</em></td>
<td>Paclitaxel <em>(Taxol)</em></td>
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<td><strong>Docetaxel</strong> <em>(Taxotere)</em></td>
<td>Vinorelbine <em>(Navelbine)</em></td>
</tr>
<tr>
<td><strong>Docetaxel</strong> <em>(Taxotere)</em></td>
<td>* = with each dose</td>
</tr>
<tr>
<td><strong>Docetaxel</strong> <em>(Taxotere)</em></td>
<td>^ = every other dose</td>
</tr>
<tr>
<td><strong>Docetaxel</strong> <em>(Taxotere)</em></td>
<td># = weekly</td>
</tr>
<tr>
<td><strong>Docetaxel</strong> <em>(Taxotere)</em></td>
<td></td>
</tr>
</tbody>
</table>
## SCR Monitoring for Chemotherapy

<table>
<thead>
<tr>
<th>Drug 1</th>
<th>Drug 2</th>
<th>Drug 3</th>
<th>Drug 4</th>
<th>Drug 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azacitadine (Vidaza)</td>
<td>Cisplatin (Platinol)*</td>
<td>Epirubicin (Ellence)</td>
<td>Methotrexate</td>
<td>Temsirolimus (Torisel)^</td>
</tr>
<tr>
<td>Bendamustine (Treanda)</td>
<td>Clofarabine (Clolar)*</td>
<td>Eribulin (Halaven)</td>
<td>Mitomycin (Mutamycin)</td>
<td>Topotecan (Hycamtin)</td>
</tr>
<tr>
<td>Bleomycin (Blenoxane)</td>
<td>Cyclophosphamide (Cytoxan)</td>
<td>Etoposide (Etopophos)</td>
<td>Oxaliplatin (Eloxatin)</td>
<td>Trabectedin (Yondelis)</td>
</tr>
<tr>
<td><em>Brentuximab (Adcetris)</em></td>
<td>Cytarabine (Ara-C)</td>
<td>Fludarabine (Fludara)</td>
<td>Pemetrexed (Alimta)*</td>
<td></td>
</tr>
<tr>
<td>Carboplatin (Paraplatin)</td>
<td>Daunorubicin (Cerubidine)</td>
<td>Idarubicin (Idamycin)</td>
<td>Pentostatin (Nipent)*</td>
<td></td>
</tr>
<tr>
<td>Carfilzomib (Kyprolis)</td>
<td>Daunorubicin/Cytarabine (Vyxeos)*</td>
<td>Gemcitabine (Gemzar)</td>
<td>Pralatrexate (Folotyn)</td>
<td></td>
</tr>
<tr>
<td>Carmustine (BiNCU)</td>
<td>Decitabine (Dacogen)</td>
<td>Ifosfamide (Ifex)</td>
<td>Streptozocin (Zanosar)#</td>
<td></td>
</tr>
</tbody>
</table>

* = with each dose  
^ = every other dose  
# = weekly
LVEF Monitoring for Chemotherapy

- **Diagnostic procedures**
  - Echocardiogram (ECHO)
  - Multigated acquisition (MUGA) scan

- **Chemotherapy induced cardiotoxicity**
  - **Definition**
    - Heart failure (HF) symptoms with $\geq 5\%$ LVEF reduction to $<55\%$
    - No HF symptoms with $\geq 10\%$ LVEF reduction to $<55\%$
  - **Type 1**
    - Cumulative dose related
    - Permanent damage
    - Ex. Anthracyclines
  - **Type 2**
    - Not cumulative dose related
    - Reversible damage
    - Ex. Trastuzumab

<table>
<thead>
<tr>
<th>Ado-trastuzumab (Kadcyla)</th>
<th>Daunorubicin (Cerubidine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daunorubicin/Cytarabine (Vyxeos)</td>
<td>Doxorubicin (Adriamycin)</td>
</tr>
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<td>Epirubicin (Ellence)</td>
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<tr>
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<td>Mitomycin (Mutamycin)</td>
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<td>Mitoxantrone (Novantrone)</td>
<td>Trabectedin (Yondelis)</td>
</tr>
</tbody>
</table>

PFT Monitoring for Chemotherapy

- Diagnostic procedures
  - Spirometry
    - Forced vital capacity (FVC)
    - Forced expiratory volume in 1 second (FEV₁)
  - Lung diffusing capacity
    - Diffusing capacity of the lung for carbon monoxide (DLCO)

<table>
<thead>
<tr>
<th>Baseline and Periodic PFTs</th>
<th>Baseline Chest X-Ray</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin (Blenoxane)</td>
<td>Bortezomib (Velcade)</td>
</tr>
<tr>
<td></td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Carmustine (BiNCU)</td>
<td>Temsirolimus (Torisel)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Consider Chest X-Ray and/or PFTs for new or worsening pulmonary symptoms</th>
</tr>
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</tr>
<tr>
<td>Methotrexate</td>
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<tr>
<td>Bortezomib <em>(Velcade)</em></td>
</tr>
<tr>
<td>Mitomycin <em>(Mutamycin)</em></td>
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<td>Cyclophosphamide <em>(Cytoxan)</em></td>
</tr>
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</tr>
<tr>
<td>Vinorelbine <em>(Navelbine)</em></td>
</tr>
<tr>
<td>Irinotecan <em>(Camptosar)</em></td>
</tr>
</tbody>
</table>

Chemotherapy Drug Classes

• **Alkylating agents**
  – Alkyl sulfonates
  – Aziridines
  – Nitrogen mustards
  – Nitrosoureas
  – Platinum agents
  – Triazenes/Methylating agents

• **Antimetabolites**
  – DNA hypomethylating agents
  – Folate antagonists
  – Pyrimidine analogs
  – Purine analogs
  – Miscellaneous: hydroxyurea

• **Antimicrotubular agents**
  – Epothilones
  – Halichondrin B analogs
  – Taxanes
  – Vinca alkaloids

• **Antitumor antibiotics**
  – Anthracyclines
  – Actinomycins
  – Miscellaneous: bleomycin, mitomycin, mitoxantrone

• **Topoisomerase inhibitors**
  – Topoisomerase I inhibitors
  – Topoisomerase II inhibitors
    • Anthracyclines
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# Alkylating Agents: Nitrogen Mustards

<table>
<thead>
<tr>
<th>Monitoring Parameters</th>
<th>Cyclophosphamide</th>
<th>Ifosfamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Myelosuppression (DLT)</td>
<td>• Myelosuppression (DLT)</td>
<td></td>
</tr>
<tr>
<td>• Hemorrhagic cystitis</td>
<td>• Hemorrhagic cystitis</td>
<td></td>
</tr>
<tr>
<td>- Acrolein metabolite accumulation</td>
<td>- Acrolein metabolite accumulation</td>
<td></td>
</tr>
<tr>
<td>- Prevention via mesna and hydration</td>
<td>- Prevention via mesna and hydration</td>
<td></td>
</tr>
<tr>
<td>• Nephrotoxicity</td>
<td>• Nephrotoxicity</td>
<td></td>
</tr>
<tr>
<td>• Nausea and vomiting</td>
<td>• Nausea and vomiting</td>
<td></td>
</tr>
<tr>
<td>- &gt;1.5 g/m²: high emetic risk</td>
<td>- &gt;2 g/m²: high emetic risk</td>
<td></td>
</tr>
<tr>
<td>- ≤1.5 g/m²: moderate emetic risk</td>
<td>- &lt;2 g/m²: moderate emetic risk</td>
<td></td>
</tr>
<tr>
<td>• Alopecia</td>
<td>• Alopecia</td>
<td></td>
</tr>
<tr>
<td>• Sterility</td>
<td>• Sterility</td>
<td></td>
</tr>
<tr>
<td>• Syndrome of inappropriate antidiuretic hormone secretion (SIADH)</td>
<td>• Neurotoxicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Chloroacetaldehyde accumulation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Consider methylene blue or thiamine treatment</td>
<td></td>
</tr>
</tbody>
</table>

DLT = Dose Limiting Toxicity

Devita, Hellman, And Rosenberg's Cancer, 2009.
## Alkylating Agents: Platinums

<table>
<thead>
<tr>
<th></th>
<th>Cisplatin</th>
<th>Carboplatin</th>
<th>Oxaliplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nephrotoxicity</strong></td>
<td>+++ (DLT)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Typically reversible</td>
<td>Calvert dosing equation: AUC x (GFR + 25)</td>
<td>CrCl &lt;30 ml/min may require dose reduction</td>
</tr>
<tr>
<td></td>
<td>Pre and post IV hydration</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mannitol, K, and Mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urine output &gt;100 mL/hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Myelosuppression</strong></td>
<td>+</td>
<td>+++ (DLT)</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Primarily anemia</td>
<td>Primarily thrombocytopenia</td>
<td>Thrombocytopenia with higher doses</td>
</tr>
<tr>
<td></td>
<td>Delayed (nadir 3-6 weeks)</td>
<td></td>
<td>Mild anemia and neutropenia</td>
</tr>
<tr>
<td><strong>Neurotoxicity</strong></td>
<td>+++</td>
<td>+</td>
<td>+++ (DLT)</td>
</tr>
<tr>
<td></td>
<td>Reversible</td>
<td>Peripheral neuropathy</td>
<td>Acute: common, reversible, and exacerbated by cold</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy is most common symptom</td>
<td>Not common</td>
<td>Delayed: irreversible, associated with cumulative dose</td>
</tr>
<tr>
<td></td>
<td>Cumulative dose &gt;300 mg/m²</td>
<td></td>
<td>Pharyngolaryngeal dysesthesias</td>
</tr>
</tbody>
</table>
# Alkylating Agents: Platinums

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<tr>
<th></th>
<th>Cisplatin</th>
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<th>Oxaliplatin</th>
</tr>
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<tbody>
<tr>
<td><strong>Nausea and Vomiting</strong></td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>• High emetic risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Acute and delayed (2-5 days post dose)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• AUC ≥4: High emetic risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• AUC &lt;4: Moderate emetic risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Moderate emetic risk</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Ototoxicity**                | +++       | +           | +           |
| • Typically irreversible       |           |             |             |
| • Cumulative dose >400 mg/m²   |           |             |             |
| • Ototoxic drug interactions   |           |             |             |

| **Hypersensitivity**           | -         | +           | +           |
| • Potentially IgE mediated     |           |             |             |
| • Delayed reaction with increased risk with >6 cycles | | | |
| • Mild: slow infusion rate and administer antihistamine and/or steroid | | | |
| • Severe: desensitization protocol | | | |
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Antimetabolites: Folate Antagonist

Methotrexate (MTX)

- Folate analog
  - Inhibits dihydrofolate reductase and thymidylate synthetase
  - Results in the cessation of DNA synthesis

- Multiple indications
  - Monotherapy
  - Component of several treatment regimens

- MTX toxicity risk factors
  - Dose
  - MTX serum levels
  - Pharmacokinetic variations
  - Pharmacogenomic variations
  - Third space fluid collections
  - Drug interactions

Image: LaCasce, AS. UpToDate, 2018.

<table>
<thead>
<tr>
<th>MTX Dose</th>
<th>Definition</th>
<th>General Indications</th>
<th>Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt; 50 mg/m²</td>
<td>• Nonmalignant disorders</td>
<td>• Gastrointestinal (GI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Central nervous system (CNS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Alopecia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Stomatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Macular rash</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Mild hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Mild myelosuppression</td>
</tr>
<tr>
<td>Intermediate</td>
<td>50 – 500 mg/m²</td>
<td>• Nonmalignant disorders</td>
<td>• Dose dependent toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Malignant disorders</td>
<td>• Generally no aggressive prophylaxis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Leucovorin rescue rarely needed at doses &lt; 250 mg/m²</td>
</tr>
<tr>
<td>High (HDMTX)</td>
<td>≥ 500 mg/m²</td>
<td>• CNS prophylaxis</td>
<td>• Considered lethal dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CNS lymphomas</td>
<td>• Renal dysfunction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Osteosarcomas</td>
<td>• Hepatic toxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Leptomeningeal metastases</td>
<td>• Myelosuppression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Gastrointestinal (GI) mucositis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Requires aggressive prophylaxis and multiple leucovorin doses</td>
</tr>
</tbody>
</table>

Leucovorin

• “Rescue” agent utilized in HDMTX regimens
  – Increases reduced cellular folate stores
  – Overcomes MTX inhibition of purine and pyrimidine synthesis

• Effective in the prevention of HDMTX toxicity
  – Nephrotoxicity
  – Myelosuppression
  – Neurotoxicity
  – Gastrointestinal toxicity

• Leucovorin rescue regimens vary
  – MTX dose and infusion duration
  – Chemotherapy indication
  – Institution specific protocols
# HDMTX Toxicity Monitoring

## Nephrotoxicity
- Direct tubular injury via MTX precipitation and constriction of afferent arteriole
- Typically reversible and recovery in 2-3 weeks
- Risk factors: volume depletion, acidic urine, and drug interactions
- Prevention:
  - IV hydration: 2.5-3.5 L/m²/day of fluids 4-12 hours prior to MTX infusion and then continuing fluids for 24-48 hours or until discharge
  - Urine alkalinization: Urine pH >7 prior to MTX initiation with IV or oral sodium bicarbonate and maintain pH >7 until MTX serum levels <0.1 μM
  - Leucovorin rescue
- Management: increase leucovorin dose and consider glucarpidase

## Hepatotoxicity
- Idiosyncratic with recovery in 1-2 weeks
- Risk factors: alcoholism, diabetes, obesity, and hepatitis B or C infection
- Prevention: avoid hepatotoxic drugs, reduce risk, and leucovorin rescue

## Pulmonary Toxicity
- Idiosyncratic reaction with low incidence (<1%) but potentially fatal
- Usually occurs within 1st year of therapy
- Folate repletion does not decrease risk
- Management: hold MTX and provide supportive care +/- corticosteroids
# HDMTX Toxicity Monitoring

<table>
<thead>
<tr>
<th>Toxicity Type</th>
<th>Description</th>
</tr>
</thead>
</table>
| **Myelosuppression** | • Pancytopenia with complete recovery around 3 weeks  
• Prevention: leucovorin rescue  
• Management: perform risk assessment to consider transfusions, granulocyte colony stimulating factor (G-CSF), and/or antibiotics |
| **Neurologic Toxicity** | • Acute encephalopathy: 12-72 hours after IV or IT MTX administration with presentation of somnolence, confusion, seizures, insomnia, or coma  
• Subacute encephalopathy: few weeks after MTX initiation with symptoms of paraplegia, cerebellar dysfunction, or seizures  
• Prevention and management: leucovorin and can consider aminophylline or dextromethorphan |
| **Emetic Risk**     | • Moderate emetic risk at doses $\geq250$ mg/$m^2$ ($5HT_3$ antagonist + corticosteroid +/- NK-1 receptor antagonist) |
| **Mucositis**       | • Presents 5-10 days after MTX  
• Prevention and management: leucovorin, lifestyle modification, analgesics, antidiarrheals, and can consider palifermin |
## Antimetabolites: Pyrimidine Analogs

### Cytarabine

<table>
<thead>
<tr>
<th>Standard Dose Monitoring</th>
<th>High Dose Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>(100-200 mg/m²/day IVCI)</td>
<td>(1.5-3 g/m²/dose)</td>
</tr>
</tbody>
</table>

- Myelosuppression (DLT)
- Low emetic risk
- Mucositis
- Diarrhea
- Alopecia

- Myelosuppression (DLT)
- Moderate emetic risk: >200 mg/m²
- Mucositis
- Diarrhea
- Alopecia

- Neurotoxicity: cerebellar dysfunction
  - Typically reversible
  - Presents 3-8 days after 1st dose
  - Loss of balance, altered muscle tone, movement disorders, speech deficits, and/or nystagmus

- Ocular toxicity: conjunctivitis
  - Prophylaxis with ophthalmic steroids
  - Dexamethasone 0.1% 1-2 drops in each eye Q6H starting 1 day prior and continued for 2-7 days after last dose

- Dermatologic toxicity: hand-foot syndrome

---

Devita, Hellman, And Rosenberg's Cancer, 2009.
### Antimetabolites: Pyrimidine Analogs

<table>
<thead>
<tr>
<th>Monitoring Parameters</th>
<th>Fluorouracil (5-FU)</th>
<th>Capecitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IV bolus or Continuous Infusion (IVCI)</td>
<td>Oral Fluorouracil Pro-drug</td>
</tr>
<tr>
<td><strong>Mucositis</strong> (IVCI DLT)</td>
<td>• Mucositis</td>
<td>• Mucositis</td>
</tr>
<tr>
<td><strong>Diarrhea</strong> (bolus &gt; IVCI)</td>
<td>• Diarrhea</td>
<td>• Diarrhea</td>
</tr>
<tr>
<td><strong>Hand-foot syndrome</strong> (IVCI only)</td>
<td>• Hand-foot syndrome</td>
<td>• Hand-foot syndrome (DLT)</td>
</tr>
<tr>
<td>- Palmar-plantar erythrodysesthesia</td>
<td>- Palmar-plantar erythrodysesthesia</td>
<td>- Palmar-plantar erythrodysesthesia</td>
</tr>
<tr>
<td>- Symptoms: redness, tenderness, peeling skin, numbness, blisters, and/or pain</td>
<td>- Symptoms: redness, tenderness, peeling skin, numbness, blisters, and/or pain</td>
<td></td>
</tr>
<tr>
<td><strong>Myelosuppression</strong> (bolus &gt; IVCI)</td>
<td>• Myelosuppression</td>
<td>• Minimal myelosuppression</td>
</tr>
<tr>
<td><strong>Low emetic risk</strong> (bolus &gt; IVCI)</td>
<td>• Low emetic risk</td>
<td>• Low emetic risk</td>
</tr>
<tr>
<td><strong>Coronary vasospasm</strong></td>
<td>• Coronary vasospasm</td>
<td>• Coronary vasospasm</td>
</tr>
<tr>
<td><strong>Radiation sensitizer</strong></td>
<td>• Radiation sensitizer</td>
<td>• Radiation sensitizer</td>
</tr>
<tr>
<td><strong>Alopecia</strong></td>
<td>• Alopecia</td>
<td>• Alopecia</td>
</tr>
<tr>
<td><strong>Nail changes</strong></td>
<td>• Nail changes</td>
<td>• Nail changes</td>
</tr>
<tr>
<td><strong>Photosensitivity</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

Antimetabolites: Pyrimidine Analogs

Fluorouracil and Capecitabine

• Dihydropyrimidine dehydrogenase (DPD) deficiency
  – Metabolizes 5-FU to inactive metabolite
  – Deficiency results in severe toxicity

• Drug interactions
  – Leucovorin enhances 5-FU anticancer effects
  – Capecitabine and warfarin black box warning: clinically significant increase in INR

• Hand-foot syndrome prevention
  – Pyridoxine
  – Moisturize hand and feet
  – Avoid pressure, tight clothing, and hot water
  – Apply sunscreen
  – Wear gloves in winter or cold environments

Chemotherapy Drug Classes

• **Alkylating agents**
  - Alkyl sulfonates
  - Aziridines
  - Nitrogen mustards
  - Nitrosoureas
  - Platinum agents
  - Triazenes/Methylating agents

• **Antimetabolites**
  - DNA hypomethylating agents
  - Folate antagonists
  - Pyrimidine analogs
  - Purine analogs
  - Miscellaneous: hydroxyurea

• **Antimicrotubular agents**
  - Epothilones
  - Halichondrin B analogs
  - Taxanes
  - Vinca alkaloids

• **Antitumor antibiotics**
  - Anthracyclines
  - Actinomycins
  - Miscellaneous: bleomycin, mitomycin, mitoxantrone

• **Topoisomerase inhibitors**
  - Topoisomerase I inhibitors
  - Topoisomerase II inhibitors
    - Anthracyclines
Chemotherapy Drug Classes

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• **Topoisomerase inhibitors**
  - Topoisomerase I inhibitors
  - Topoisomerase II inhibitors
    • Anthracyclines
# Antimicrotubular Agents: Taxanes

<table>
<thead>
<tr>
<th>Monitoring Parameters</th>
<th>Docetaxel</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Myelosuppression (DLT)</td>
<td>• Myelosuppression (DLT)</td>
</tr>
<tr>
<td></td>
<td>- Mostly neutropenia</td>
<td>- Mostly neutropenia</td>
</tr>
<tr>
<td></td>
<td>• Fluid retention (dose dependent)</td>
<td>- Increased with longer infusion</td>
</tr>
<tr>
<td></td>
<td>- Dexamethasone 8 mg PO BID for 3 days, starting 1 day prior to docetaxel</td>
<td>- Due to cremophor solvent</td>
</tr>
<tr>
<td></td>
<td>• Hypersensitivity reaction</td>
<td>- Steroid + H1RA + H2RA premedication</td>
</tr>
<tr>
<td></td>
<td>- Due to polysorbate 80</td>
<td>• Peripheral neuropathy (cumulative dose)</td>
</tr>
<tr>
<td></td>
<td>- Dexamethasone premedication</td>
<td>- Increased with shorter infusion</td>
</tr>
<tr>
<td></td>
<td>- Slow infusion rate for mild reaction</td>
<td>• Mucositis</td>
</tr>
<tr>
<td></td>
<td>• Neuropathy (cumulative dose)</td>
<td>• Alopecia</td>
</tr>
<tr>
<td></td>
<td>• Mucositis</td>
<td>• Low emetic risk</td>
</tr>
<tr>
<td></td>
<td>• Alopecia</td>
<td>• Myalgia</td>
</tr>
<tr>
<td></td>
<td>• Low emetic risk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cutaneous reaction</td>
<td></td>
</tr>
</tbody>
</table>
# Antimicrotubular Agents: Vinca Alkaloids

<table>
<thead>
<tr>
<th></th>
<th>Vincristine</th>
<th>Vinblastine</th>
<th>Vinorelbine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common Indications</strong></td>
<td>• Leukemia</td>
<td>• Lymphomas and testicular cancer</td>
<td>• Lung cancer</td>
</tr>
<tr>
<td></td>
<td>• Max dose = 2 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Monitoring Parameters</strong></td>
<td>• Neurotoxicity (DLT)</td>
<td>• Least neurotoxic</td>
<td>• Less neurotoxic</td>
</tr>
<tr>
<td></td>
<td>• No myelosuppression</td>
<td>• Myelosuppression (DLT)</td>
<td>• Myelosuppression (DLT)</td>
</tr>
<tr>
<td></td>
<td>• Constipation</td>
<td>• Constipation</td>
<td>• Constipation</td>
</tr>
<tr>
<td></td>
<td>• Alopecia</td>
<td>• Alopecia</td>
<td>• Alopecia</td>
</tr>
<tr>
<td></td>
<td>• Minimal emetic risk</td>
<td>• Minimal emetic risk</td>
<td>• Minimal emetic risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hypertension</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Considerations</strong></td>
<td>• Implement bowel regimen pre and post vinca alkaloid dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Extravasation management (vesicant)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Stop infusion immediately</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Elevate affected extremity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Apply warm dry compresses for 20 minutes 4x/day for 1-2 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Administer hyaluronidase 1 mL (150 units/mL) as 5 separate 0.2 mL injections subcutaneously into extravasation site</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• FATAL if given intrathecally</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Dispense vinca alkaloids in a minibag of compatible solution and NOT in a syringe (ISMP)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Chemotherapy Drug Classes

• **Alkylating agents**
  – Alkyl sulfonates
  – Aziridines
  – Nitrogen mustards
  – Nitrosoureas
  – Platinum agents
  – Triazenes/Methylating agents

• **Antimetabolites**
  – DNA hypomethylating agents
  – Folate antagonists
  – Pyrimidine analogs
  – Purine analogs
  – Miscellaneous: hydroxyurea

• **Antimicrotubular agents**
  – Epothilones
  – Halichondrin B analogs
  – Taxanes
  – Vinca alkaloids

• **Antitumor antibiotics**
  – Anthracyclines
  – Actinomycins
  – Miscellaneous: bleomycin, mitomycin, mitoxantrone

• **Topoisomerase inhibitors**
  – Topoisomerase I inhibitors
  – Topoisomerase II inhibitors
    • Anthracyclines
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  - Topoisomerase I inhibitors
  - Topoisomerase II inhibitors
    - Anthracyclines
# Antitumor Antibiotics: Anthracyclines

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Doxorubicin</th>
<th>Daunorubicin</th>
<th>Idarubicin</th>
<th>Epirubicin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicities</td>
<td>• Myelosuppression (DLT)</td>
<td>• Myelosuppression (DLT)</td>
<td>• Myelosuppression (DLT)</td>
<td>• Myelosuppression (DLT)</td>
</tr>
<tr>
<td></td>
<td>• Cardiotoxicity</td>
<td>• Cardiotoxicity</td>
<td>• Less cardiotoxicity</td>
<td>• Less cardiotoxicity</td>
</tr>
<tr>
<td></td>
<td>• More severe mucositis</td>
<td>• Mucositis</td>
<td>• Mucositis</td>
<td>• Mucositis</td>
</tr>
<tr>
<td></td>
<td>• Mod to high emetic risk</td>
<td>• Moderate emetic risk</td>
<td>• Moderate emetic risk</td>
<td>• Mod to high emetic risk</td>
</tr>
<tr>
<td></td>
<td>• Alopecia</td>
<td>• Alopecia</td>
<td>• Alopecia</td>
<td>• Alopecia</td>
</tr>
<tr>
<td></td>
<td>• Red/orange urine</td>
<td>• Red/orange urine</td>
<td>• Red/orange urine</td>
<td>• Red/orange urine</td>
</tr>
<tr>
<td></td>
<td>• Radiation recall</td>
<td>• Radiation recall</td>
<td>• Radiation recall</td>
<td>• Radiation recall</td>
</tr>
<tr>
<td>Max Lifetime Dose</td>
<td>• 500 mg/m²</td>
<td>• 550 mg/m²</td>
<td>• 150 mg/m²</td>
<td>• 900 mg/m²</td>
</tr>
<tr>
<td>Clinical</td>
<td>• Extravasation management (vesicant)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Stop infusion immediately</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Elevate affected extremity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Apply cold dry compresses for 20 minutes 4x/day for 1-2 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Apply topical DMSO to a region covering twice the affected area every 8 hours for 7 days (do not cover with dressing)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dexrazoxane 1000 mg/m² on days 1-2, followed by 500 mg/m² on day 3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Anthracycline Cardiotoxicity

• **Mechanism**
  - Cardiomyocyte damage via oxygen free radicals

• **Risk factors**
  - Cumulative dose
  - Age >65 years
  - Female gender
  - African Americans
  - Hypertension
  - Cardiac disease
  - Low baseline LVEF
  - Radiation or cardiotoxic drug exposure

• **Cardiotoxic effects**
  - Acute rhythm disruptions
  - Chronic heart failure

• **Cardioprotective agents (EF 40-49%)**
  - Dexrazoxane (Zinecard®)
    - Chelating agent interfering with iron mediated oxygen free radical generation
    - IV: 10:1 ratio of dexrazoxane:doxorubicin
  - Beta blockers: carvedilol or nebivolol
  - Angiotensin inhibition: enalapril or candesartan
  - Consider statin

Antitumor Antibiotics: Bleomycin

• Pulmonary toxicity (DLT)
  – Oxygen free radical formation
  – Potentially life-threatening interstitial pulmonary fibrosis
• Administration
  – Anaphylactic reaction: consider test dose
  – Fever and chills: acetaminophen premedication
• Mucositis
• Alopecia
• Cutaneous reactions
  – Hyperpigmentation
  – Erythema
  – Skin peeling

Pulmonary Toxicity Risk Factors

- Cumulative dose >400 units (Max lifetime dose = 400 units)
- Age >40 years
- Smoking
- Chest irradiation
- Concurrent use of G-CSF
Chemotherapy Drug Classes

- **Alkylating agents**
  - Alkyl sulfonates
  - Aziridines
  - Nitrogen mustards
  - Nitrosoureas
  - Platinum agents
  - Triazenes/Methylating agents

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  - DNA hypomethylating agents
  - Folate antagonists
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  - Miscellaneous: hydroxyurea

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  - Topoisomerase I inhibitors
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  - Topoisomerase I inhibitors
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Topoisomerase Inhibitor I: Irinotecan

• **Myelosuppression (DLT)**
  – Increased risk of neutropenia in patients with homozygous UGT1A1*28 allele
  – Decrease starting dose by at least one dose level

• **Diarrhea (DLT)**
  – Acute diarrhea (<24 hours): inhibition of acetylcholinesterase
    • Premedicate with atropine 0.25-1 mg IV or subcutaneously x 1
  – Delayed diarrhea (>24 hours): mucosal cytotoxicity
    • Loperamide 4 mg PO x 1 dose, then 2 mg every 2 hours until no diarrhea for 12 hours
    • Octreotide 100-150 mcg IV or subcutaneously every 8 hours

• **Acute cholinergic effect**
  – Symptoms include flushing, sweating, abdominal cramps, and/or diarrhea
  – Premedicate with atropine 0.25-1 mg IV or subcutaneously x 1

• **Moderate emetic risk**

• **Alopecia**
Question #1

• Which of the following chemotherapy agents is NOT correctly paired with its dose limiting toxicity?

A. Cisplatin: Nephrotoxicity
B. Vincristine: Neurotoxicity
C. Doxorubicin: Mucositis
D. Bleomycin: Pulmonary toxicity
E. Irinotecan: Diarrhea
Question #2

- Which of the following methods is NOT utilized for the primary prevention of HDMTX nephrotoxicity?

A. Aggressive fluid hydration
B. Urine alkalization via sodium bicarbonate
C. Leucovorin rescue
D. Glucarpidase therapy
Immunotherapy
Cancer Immunotherapy

• Type of therapy utilizing the immune system to elicit an anti-tumor response
• Passive immunotherapy: enhance existing immune system anti-tumor response
  – Immunomodulating antibodies
    • Immune co-stimulatory antibodies
    • Immune checkpoint inhibitors
  – Adoptive immunotherapy
    • Tumor infiltrating lymphocyte
    • Genetically modified T-cell receptors (TCRs)
    • Chimeric antigen receptors (CARs)
• Active immunotherapy: stimulate immune system response to attack cancer cells
  – Specific
    • Vaccines
    • Oncolytic viruses
  – Non-specific
    • Cytokines
Cancer Immunotherapy

- Type of therapy utilizing the immune system to elicit an anti-tumor response
- Passive immunotherapy: enhance existing immune system anti-tumor response
  - Immunomodulating antibodies
    - Immune co-stimulatory antibodies
    - Immune checkpoint inhibitors
  - Adoptive immunotherapy
    - Tumor infiltrating lymphocyte
    - Genetically modified T-cell receptors (TCRs)
    - Chimeric antigen receptors (CARs)
- Active immunotherapy: stimulate immune system response to attack cancer cells
  - Specific
    - Vaccines
    - Oncolytic viruses
  - Non-specific
    - Cytokines
Antitumor Monoclonal Antibodies

- Antibody source
  - Murine/mouse (-omab)
  - Chimeric (-ximab)
  - Humanized (-zumab)
  - Human (-umab)

- Naked monoclonal antibodies
  - No modifications
  - Mechanism of action varies depending on molecular target

- Conjugated monoclonal antibodies
  - Combined with chemotherapy or radioactive agent
  - Deliver agent directly to cancer cell

- Bispecific monoclonal antibodies
  - Single agent comprised of two different monoclonal antibodies

Devita, Hellman, And Rosenberg’s Cancer, 2009.
Immunotherapy Toxicity Overview

Patient
- Cancer type
- Comorbidities
- Organ function
- Performance status

Monoclonal Antibodies
- Drug mechanism of action
- Drug dose
- Drug schedule
- Monotherapy or combination regimen with chemotherapy

Toxicities
- Myelosuppression
- Hepatic
- Renal
- Cardiovascular
- Pulmonary
- Gastrointestinal
- Neurological
- Dermatological
- Musculoskeletal
- Endocrine
- Pancreatic
- Ocular
- Infusion related
Lab Monitoring
# CBC Monitoring for Immunotherapy

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Ado-trastuzumab (Kadcyla)</strong>*</td>
<td>Durvalumab (Imfinzi)*</td>
<td>Olaratumab (Lartruvo)*</td>
</tr>
<tr>
<td>Atezolizumab (Tecentriq)^</td>
<td><strong>Gemtuzumab (Mylotarg)</strong>*</td>
<td>Pembrolizumab (Keytruda)^</td>
</tr>
<tr>
<td>Bevacizumab (Avastin)*</td>
<td>Nivolumab (Opdivo)^</td>
<td>Ramucirumab (Cyramza)*</td>
</tr>
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<td>Obinutuzumab (Gazyva)*</td>
<td>Rituximab (Rituxan)</td>
</tr>
<tr>
<td>Daratumumab (Darzalex)*</td>
<td>Ofatumumab (Arzerra)</td>
<td></td>
</tr>
</tbody>
</table>

* = with each dose  
^ = every other dose  
# = weekly
# LFT Monitoring for Immunotherapy

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<thead>
<tr>
<th>Ado-trastuzumab (Kadcyla)*</th>
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<td>Brentuximab (Adcetris)*</td>
<td>Ipilimumab (Yervoy)*</td>
<td>Pembrolizumab (Keytruda)^</td>
</tr>
<tr>
<td>Durvalumab (Imfinzi)*</td>
<td>Nivolumab (Opdivo)^</td>
<td></td>
</tr>
</tbody>
</table>

* = with each dose
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# = weekly
Lab Monitoring for Immunotherapy

**Serum Creatinine**
- *Brentuximab (Adcetris)*
- Durvalumab (Imfinzi)*
- Nivolumab (Opdivo)^
- Obinutuzumab (Gazyva)*
- Pembrolizumab (Keytruda)^

**Ejection Fraction**
- (Baseline and every 3 months)
- *Ado-trastuzumab (Kadcyla)*
- Pertuzumab (Perjeta)
- Trastuzumab (Herceptin)

**Electrolytes**
- (Mg/Ca/K at baseline, during treatment, and 8 weeks after treatment)
- Cetuximab (Erbitux)

**Thyroid Function Tests**
- (Baseline and periodically)
- Atezolizumab (Tecentriq)
- Durvalumab (Imfinzi)
- Ipilimumab (Yervoy)
- Nivolumab (Opdivo)
- Pembrolizumab (Keytruda)
- Ramucirumab (Cyramza)

* = with each dose
^ = every other dose
# = weekly
Lab Monitoring for Immunotherapy

- **Hepatitis B virus (HBV) panel**
  - Required prior to anti-CD20 monoclonal initiation
    - Box warning: risk for HBV reactivation resulting in fulminant hepatitis, hepatic failure, or death
    - Serology: hepatitis B surface antigen (HBsAg) and total hepatitis B core antibody (anti-HBc)
  - HBV reactivation occurs: discontinue anti-CD20 monoclonal

- **Urine protein**
  - Bevacizumab is associated with proteinuria and nephrotic syndrome
  - <2+ urine dipstick: continue to monitor
  - >2+ urine dipstick: further assessment via 24 hour urine collection
    - >2 g protein in 24 hours: stop bevacizumab and monitor
    - <2 g protein in 24 hours: restart bevacizumab
  - Nephrotic syndrome: discontinue bevacizumab

### Hepatitis B Panel
- Obinutuzumab (Gazyva)
- Ofatumumab (Arzerra)
- Rituximab (Rituxan)

### Urine Protein
- Bevacizumab (Avastin)*
Monoclonal Antibodies: Targeted Therapy
## Immunotherapy: Targeted Therapy

### Rituximab (Rituxan)

<table>
<thead>
<tr>
<th>Indications</th>
<th>Lymphomas, leukemias, and autoimmune disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>CD20 surface antigen on B-lymphocytes</td>
</tr>
<tr>
<td>Mechanism</td>
<td>CD20 antigen binding results in complement dependent B-cell cytotoxicity and lysis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Monitoring Parameters</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBV reactivation</strong></td>
<td>- HBV screening prior to initiation</td>
</tr>
<tr>
<td></td>
<td>- HBsAg and Anti-HBc</td>
</tr>
<tr>
<td><strong>Hypersensitivity reactions</strong></td>
<td>- Hypotension, angioedema, bronchospasm, and/or urticaria</td>
</tr>
<tr>
<td></td>
<td>- 80% of fatal reactions occurred with first infusion</td>
</tr>
<tr>
<td><strong>Infusion related reactions</strong></td>
<td>- Chills, fever, rigors, dizziness, rash, and/or nausea/vomiting</td>
</tr>
<tr>
<td></td>
<td>- Pretreatment: acetaminophen + diphenhydramine +/- steroids</td>
</tr>
<tr>
<td><strong>Mucocutaneous reactions</strong></td>
<td>- Stevens-Johnson syndrome, toxic epidermal necrolysis, and others</td>
</tr>
<tr>
<td><strong>Lymphopenia</strong></td>
<td>- Avoid live vaccines during treatment</td>
</tr>
</tbody>
</table>

---

# Immunotherapy: Targeted Therapy

## Bevacizumab (Avastin)

<table>
<thead>
<tr>
<th>Indications</th>
<th>• Colorectal, cervical, ovarian, renal, lung cancer, and glioblastoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>• Vascular endothelial growth factor (VEGF)</td>
</tr>
<tr>
<td>Mechanism</td>
<td>• Binds to VEGF and inhibits angiogenesis</td>
</tr>
<tr>
<td></td>
<td>• Reduces proliferation of endothelial cells</td>
</tr>
<tr>
<td>Monitoring Parameters</td>
<td></td>
</tr>
<tr>
<td>Severe or fatal hemorrhage</td>
<td>• Bleeding episodes 5x greater in bevacizumab patients</td>
</tr>
<tr>
<td></td>
<td>• Hemoptysis, epistaxis, GI bleed, CNS bleed, or vaginal bleed</td>
</tr>
<tr>
<td></td>
<td>• Avoid in patients with recent history of hemoptysis</td>
</tr>
<tr>
<td>GI perforation</td>
<td>• Incidence: 0.3 - 3%</td>
</tr>
<tr>
<td>Wound healing impairment</td>
<td>• Withhold bevacizumab for at least 28 days prior to surgery</td>
</tr>
<tr>
<td></td>
<td>• Do not administer for at least 28 days after surgery and until wound has healed</td>
</tr>
<tr>
<td>Hypertension</td>
<td>• May cause or worsen hypertension</td>
</tr>
<tr>
<td></td>
<td>• Treat with anihypertensives (consider ACE-i or ARB if proteinuria)</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>• Caution before initiating if patient has new thrombosis</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>• Monitor prior to each dose</td>
</tr>
</tbody>
</table>

## Immunotherapy: Targeted Therapy

### Trastuzumab (Herceptin)

<table>
<thead>
<tr>
<th>Indications</th>
<th>• Breast and gastric cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>• Human epidermal growth factor receptor 2 (HER-2)</td>
</tr>
<tr>
<td>Mechanism</td>
<td>• Binds to HER-2 inducing cytotoxicity of cells overexpressing HER-2 protein</td>
</tr>
<tr>
<td>Monitoring Parameters</td>
<td></td>
</tr>
</tbody>
</table>
| Cardiomyopathy (DLT) | • Type II: reversible damage and not related to cumulative dose  
• Evaluate LVEF prior to and during treatment  
• Highest risk in patient receiving concomitant anthracycline |
| Infusion reactions   | • Serious and fatal reactions can occur  
• Fever, chills, rash, dizziness, pain, nausea, dyspnea, and/or hypotension  
• Symptoms occur during or within 24 hours of administration |
| Pulmonary toxicity   | • Dyspnea, hypoxia, interstitial pneumonitis, pleural effusion, edema, and/or pulmonary fibrosis  
• Use with caution in pre-existing pulmonary disease or tumor |
Question #3

Which of the following immunotherapy agents is NOT correctly paired with its key lab monitoring parameter?

A. Brentuximab: Complete blood count
B. Trastuzumab: Ejection fraction
C. Cetuximab: Thyroid function tests
D. Rituximab: Hepatitis B panel
E. Bevacizumab: Urine protein
Monoclonal Antibodies: Checkpoint Inhibitors
Immune Checkpoint Inhibitors

• Mechanism of action
  – Immune system homeostasis
    • Checkpoint proteins used to differentiate between normal and foreign cells
    • Immune response requires activation or inactivation of checkpoint proteins
  – Cancer cells evade immune antitumor response by utilizing checkpoint proteins
  – Checkpoint inhibitors enhance immune antitumor recognition and response

• T-cell checkpoint targets
  – Programmed cell death-1 (PD-1)
  – PD-1 ligand (PD-L1)
  – Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)
## Immunotherapy: Checkpoint Inhibitors

### Ipilimumab (Yervoy)

<table>
<thead>
<tr>
<th>Indications</th>
<th>Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Cytotoxic T-lymphocyte associated antigen 4 (CTLA-4)</td>
</tr>
</tbody>
</table>
| **Mechanism** | Binds and inhibits CTLA-4, resulting in enhanced T-cell activation and proliferation  
|          | Combination therapy with nivolumab provides synergistically superior T-cell enhancement |

### Nivolumab (Opdivo) and Pembrolizumab (Keytruda)

<table>
<thead>
<tr>
<th><strong>Nivolumab Indications</strong></th>
<th>Colorectal, head and neck, hepatic, renal, urothelial, lung cancer, melanoma, and Hodgkin lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pembrolizumab Indications</strong></td>
<td>Gastric, head and neck, urothelial, lung cancer, melanoma, and Hodgkin lymphoma</td>
</tr>
<tr>
<td><strong>Target</strong></td>
<td>Programmed cell death 1 (PD-1)</td>
</tr>
</tbody>
</table>
| **Mechanism**              | Binds to PD-1 receptor, which prevents PD-L1 from binding  
|                          | Results in T-cell activation and proliferation |

Immune Checkpoint Inhibitor Toxicity

- **Toxicity**
  - Relatively delayed onset
  - Inflammation
  - Autoimmune nature

- **Pathophysiology**
  - Unknown mechanism
  - Potentially due to T-cell activity on tumor and healthy cells
Immune Checkpoint Inhibitor Toxicity

- Incidence of immune related adverse events (irAE)
  - CTLA-4 inhibitors
    - Any grade irAE: 72%
    - High grade irAE: 24%
    - Fatal irAE: 1.08%
    - irAE seem dose dependent
  - PD-1/PD-L1 inhibitors
    - Any grade irAE: 30%
    - High grade irAE: 6%
    - Fatal irAE: 0.37%
    - irAE less dose dependent and vary by disease site

<table>
<thead>
<tr>
<th>CLTA-4, PD-1, and PD-L1 Common Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion reactions</td>
</tr>
<tr>
<td>Chills</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Colitis</td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Pruritus</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Hepatitis</td>
</tr>
<tr>
<td>Endocrine</td>
</tr>
</tbody>
</table>

## Checkpoint Inhibitor Toxicity Management

<table>
<thead>
<tr>
<th>CTCAE Criteria</th>
<th>irAE Severity</th>
<th>General Management Strategy</th>
</tr>
</thead>
</table>
| Grade 1        | • Asymptomatic         | • Observation  
• Mild symptoms                                                   | • No intervention required |
| Grade 2        | • Moderate symptoms    | • Consider holding therapy and provide local or noninvasive intervention                      |   |
|                |                        |   - Resume therapy when symptoms and/or labs decrease below grade 1                           |   |
|                |                        |   - If symptoms >1 week: initiate prednisone 0.5 - 1 mg/kg/day                              |   |
|                |                        |   - If symptoms >6 weeks: permanently discontinue therapy                                    |   |
| Grade 3        | • Several symptoms     | • Stop immunotherapy, consider hospitalization, and start high dose steroids                  |   |
|                | • Medically significant|   - Prednisone 1 - 2 mg/kg/day or equivalent (taper when grade 1)                             |   |
|                |                        |   - If patient receives prednisone >20 mg/day x 4 weeks: PCP prophylaxis                      |   |
|                |                        |   - Consider alternative immunosuppressive agents if symptoms >3 days on IV steroids: infliximab 5 mg/kg, mycophenolate mofetil, or other agents |   |
| Grade 4        | • Life threatening     | • Permanently stop immunotherapy, require hospitalization, high dose steroids                 |   |
|                |                        |   - Prednisone 2 mg/kg/day or equivalent (taper when grade 1)                                 |   |
|                |                        |   - If patient receives prednisone >20 mg/day x 4 weeks: PCP prophylaxis                      |   |
|                |                        |   - Consider alternative immunosuppressive agents based on toxicity if needed: infliximab, mycophenolate, cyclophosphamide, cyclosporine, IVIG, or others |   |
| Grade 5        | • Death due to AE      |                                                                                               |   |

Questions?
Monitoring Parameters for Chemotherapy and Immunotherapy

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Oncology Clinical Pharmacist
Piedmont Columbus Regional
References

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• DeVita V, Lawrence T, Rosenberg S. Devita, Hellman, And Rosenberg's Cancer: Principles & Practice of Oncology. 9th Ed. Lippincott Williams & Wilkins; 2009.
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